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Antioxidant Intake and Pancreatic Cancer Risk: the VITamins And Lifestyle (VITAL) Study

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Abstract

Background—Oxidative stress causes damage to many components of human cells (i.e., proteins, lipids, and DNA) and is involved in carcinogenesis. Nutrients with antioxidant properties may protect against oxidative stress. We examined intake of antioxidants from diet and supplements in relation to pancreatic cancer risk among participants of the VITamins And Lifestyle (VITAL) Study.

Methods—Participants were 77,446 men and women, ages 50–76 years, who were residents of western Washington State and completed a baseline questionnaire between 2000 and 2002. Participants reported usual diet over the past year and use of supplements over the past 10 years, in addition to demographic and lifestyle factors. During a median follow-up of 7.1 years, 184 participants developed pancreatic adenocarcinoma. Cox regression models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for seven antioxidants: β-carotene, lutein and zeaxanthin, lycopene, vitamin C, vitamin E, selenium and zinc.

Results—We observed an inverse association between dietary selenium and pancreatic cancer risk (medium vs. low intake: HR 0.58, 95% CI 0.35–0.94; high vs. low intake: HR 0.44, 95% CI 0.23–0.85; p-trend = 0.01); however, when supplemental and dietary exposures were combined, the association was no longer statistically significant.

Conclusions—Dietary selenium intake is inversely associated with risk of pancreatic cancer and the observed association is attenuated by selenium supplementation.

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Keywords

Pancreatic cancer; antioxidant; selenium; dietary intake; supplement use

INTRODUCTION

Despite discouraging results from randomized trials [1–3], there remains an interest in antioxidant nutrients and cancer risk. Antioxidants have been found to reduce oxidative DNA damage and genetic mutations [4–6] and may protect against pancreatic carcinogenesis. Epidemiological data have shown inconsistent results regarding the relation between antioxidant intake and pancreatic cancer risk. Most case-control studies [7–15] have observed an inverse association between dietary intake of vitamin C, vitamin E or β-carotene; whereas other case-control studies [16–19] and all prospective studies [20–22] have shown null results. One cohort study [20] and two meta-analysis of clinical trials [23, 24] have examined antioxidant supplementation and pancreatic cancer, and all of them found null associations.

We examined pancreatic cancer risk associated with intake of seven antioxidant nutrients, including β carotene, lutein and zeaxanthin, lycopene, vitamin C, vitamin E, selenium and zinc from dietary and supplemental sources in a large population-based prospective study, the VITamins And Lifestyle (VITAL) cohort. We hypothesized that intake of antioxidants would be inversely related to incidence of pancreatic cancer.

MATERIALS AND METHODS

Study population

Participants were members of the VITAL cohort, a population-based prospective study designed specifically to investigate the association between vitamin, mineral, and other dietary supplements and cancer risk. Details of the study design, recruitment and study implementation have been reported previously [25]. Briefly, men and women ages 50–76 years at baseline, who lived in the 13-county region in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry, were eligible to participate. Between October 2000 and December 2002, baseline questionnaires, followed by postcard reminders two weeks later, were mailed to 364,418 individuals based on a commercial mailing list. Among these, 77,719 (21.3%) were returned and deemed eligible. The study was approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill and the Fred Hutchinson Cancer Research Center (Seattle, WA).

Exposure assessment

Diet—Diet was assessed by a semi-quantitative food frequency questionnaire that captured the consumption frequency and portion size of 120 foods and beverage items over the last year and included adjustment questions on types of foods and preparation techniques [25]. Average dietary nutrient intake per day was estimated by the food frequency questionnaire analytic program based on nutrient values from the Minnesota Nutrient Data System [26].

Supplement use—Respondents were queried about multivitamin use and their intakes of 16 vitamins and minerals from all other mixtures and single supplements during the 10-year period prior to baseline, including duration in years, frequency in days/week and dose. 10-year average supplemental nutrient intake per day was computed as (dose per day) × (days per week/7) × (years/10), summed over individual supplements and micronutrient dose in participant-reported multivitamins. The VITAL supplement questionnaire showed excellent

reliability in a 3-month test-retest reliability sub-study of 220 randomly selected participants with intraclass-correlation coefficients ranging from 0.69 to 0.87 [27].

Total nutrition intake—Total nutrient intake per day was calculated by combining data on the supplement use and dietary intake. Conversion factors were used for β-carotene [28] and vitamin E [29] to account for different chemical forms or differences in absorption. The total nutrient intake was not calculated for lutein+zeaxanthin and lycopene because supplement use information was available only in pills/day while the dietary intake was in mcg/day.

Covariates—As part of the baseline questionnaire, participants also reported on personal characteristics including age, gender, ethnicity, education, height, weight, recreational physical activity, cigarette smoking, alcohol consumption, family history of cancer, and medical history. From data on height and weight, we calculated body mass index (BMI; kg/m^2). Average total metabolic equivalent (MET) hours per week over the past 10 years were calculated using the years, frequency, and published energy expenditure for different activities. Cigarette smoking status was categorized as never, former (quit>10 years), recent (quit<=10 years) and current.

Case ascertainment and follow-up

Cohort members were followed for incidence of pancreatic cancer from enrollment to December 31, 2008; the median follow-up time was 7.1 years. Incident pancreatic cancer was ascertained by linking the study cohort to the western Washington SEER cancer registry. All incident cancer cases except non-melanoma skin cancer diagnosed within the 13-county area of western Washington State are reported to SEER. We ascertained 195 incident pancreatic cancer cases including 184 adenocarcinoma (ICD-O-3 code C250–C259, C25.0–C25.3 or C25.7–C25.9) and 11 neuroendocrine tumors (C25.4). The remaining participants were right-censored from the analysis at the earliest date of the following events: withdrawal (22), emigration out of SEER catchment area (4,216), death (5,234) or 31 December 2008 (67,790).

Exclusions

For the present study, participants were excluded if they reported a positive (n=49) or missing (n=213) history of pancreatic cancer at baseline. Eleven neuroendocrine tumors were also excluded, leaving 77,446 participants in the study. In addition, participants were excluded from the dietary analysis if they did not complete all pages of the food frequency section (at least five items per page), if their energy intake was below 800 kcal for men or 600 kcal for women, or if their energy intake was above 5000 kcal for men and above 4000 kcal for women (n=7132), leaving 70,332 participants in the dietary analysis. Participants were excluded from the supplement analysis if they did not provide usage information of that supplement. Participants were excluded from the analysis of combining dietary intake and supplement use if either was missing.

Statistical analysis

Cox proportional hazards models were used to estimate crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) associated with antioxidant intake. For dietary intake and total intake, the exposure was categorized as tertiles. For supplement use, the intake levels were categorized as none, low (below median among users) and high (above median among users). P-values for trend (P-trend) were calculated by using the continuous variables with excluding values above 98th percentile for each exposure.

We selected *a priori* potential confounders for the adjusted models: age (continuous), gender, ethnicity (white, non-white), education (<=high school graduate, some college, college or advanced degree), total energy intake (tertiles), BMI (<25, 25–30, >=30 kg/m^2), recreational physical activity (tertiles of MET for all recreational activities), cigarette smoking status (never, former, recent, current), total alcohol consumption (tertiles of average daily alcohol intake), family history of pancreatic cancer (yes/no) and use of medication for diabetes (yes/no). Adding history of pancreatitis and pack-years of smoking in the models did not change results materially thus they were not included in the final models. Total energy intake was dropped from the supplement-use models because it did not change the estimates. Missing values for covariates (9% with one or more covariates missing) were imputed by chained equations in IVEware 0.2 (2012 University of Michigan). All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The cohort of participants included in this analysis was 52% female and 93% white. The average age of the participants was 62 years at baseline (Table 1).

Table 2 shows the associations between average dietary antioxidant consumption and pancreatic cancer risk. After adjustment for all *a priori* confounders, we observed a statistically significant inverse association between dietary selenium intake and risk of pancreatic cancer (HR (95% CI) for medium vs. low intake: 0.58 (0.35–0.94), high vs. low intake: 0.44 (0.23–0.85), p-trend = 0.01). The crude HR and adjusted HR are very close except for lycopene, vitamin C and selenium. Stepwise examination found that the difference for lycopene was mainly due to adjustment for age (age was negatively correlated with dietary lycopene intake, $r = -0.05$, $p<0.0001$), the difference for vitamin C was mainly due to adjustment for smoking [current smokers and recent quitters had a significantly lower intake of vitamin C (mean 104.3 mg/day) than never smokers (mean 125.5 mg/day) and long-term quitters (mean 125.5 mg/day) (ANOVA p-value <0.0001)], and the difference for the trace element selenium was mainly due to adjustment for total energy intake (total energy intake was highly correlated with dietary selenium intake, $r = 0.88$, p-value<0.0001).

Table 3 shows associations between 10-year antioxidant exposure from supplement sources and pancreatic cancer risk. In this study, most of the supplemental nutrient intake was from multivitamins except for vitamin C and vitamin E; therefore, supplement use results for vitamin C, vitamin E and multivitamins are presented in the Table. We observed no associations between use of any individual supplement or multivitamin supplements and pancreatic cancer. For supplemental selenium (mainly from multivitamins), the adjusted HRs (95% CI) were: 0.99 (0.70–1.41) for low intake (<20 mcg/day) and 0.73 (0.51–1.06) for high intake (≥20 mcg/day) vs. non-user, and the P-trend was 0.60.

When dietary and supplement uses of antioxidants were combined (Table 4), a significant inverse association was seen among those who consumed a medium level of selenium (HR: 0.59; 95% CI: 0.37–0.93), but not among those in the highest tertile of selenium intake (HR: 0.69; 95%CI: 0.39–1.20) (Table 4). Trend test were suggestive of a possible inverse association between total β-carotene intake and pancreatic cancer risk (P-trend=0.03), but the HR did not reach statistical significance for either medium or high level of intake.

DISCUSSION

In this cohort study, we investigated the intake of seven antioxidants from dietary and supplement sources in relation to pancreatic cancer risk. Our results provided evidence that

dietary selenium intake is inversely associated with risk of pancreatic cancer. We did not observe strong evidence with intake of other antioxidants.

Epidemiological studies have indicated an inverse relation between selenium intake and the incidence of certain cancers, such as colorectal cancer [30], bladder cancer [31], lung cancer [32], and prostate cancer [33], although the results were not all consistent [34]. A cancer prevention trial in Finland [22] assessed baseline dietary selenium intake with a dietary history questionnaire and found no association with pancreatic cancer risk. A recent study with the European Prospective Investigation of Cancer (EPIC) cohort in UK where dietary selenium was assessed using 7-day food diaries at baseline found that high intake of selenium was associated with a reduced risk of pancreatic cancer [35]. Moreover, two studies have identified an inverse association between biomarkers of selenium and pancreatic cancer risk, including a small nested case-control study with 22 cases and 44 controls using serum [36] and a recent case-control study with 118 cases and 399 controls using toenails [37]. In line with these biomarker studies, our study found that selenium intake from diet was inversely associated with pancreatic cancer, even after adjustment for a number of potential confounding variables. We also found that selenium supplementation does not appear to provide additional benefit beyond the effect observed for dietary intake of selenium alone, as the analysis of selenium supplement use (intake mostly from multivitamin supplements) showed null results and the association between selenium intake and pancreatic cancer was substantially attenuated and became statistically non-significant when supplemental selenium was added to dietary selenium as the exposure.

Selenium is a trace element essential to human health. It plays an important role in thyroid hormone metabolism, antioxidant defense systems and immune function [38]. Selenium has several anti-carcinogenic mechanisms including inactivating oxygen free radicals, initiating DNA repair, and inducing apoptosis [39]. However, animal and in-vitro studies have also shown that selenium promotes malignant cell transformation and protects tumor cells from stress-induced apoptosis [40]. Furthermore, a randomized trial of supplemental selenium found that selenium supplementation was linked to increased risk of type 2 diabetes mellitus [41], a risk factor for pancreatic cancer. Our results suggest that there might be an optimal range of selenium level that maximizes its anti-carcinogenicity or reduce the carcinogenicity. Further investigation is necessary to confirm this finding and determine the optimal dose. A study in British adults observed that higher selenium status was associated with adverse blood lipid profile [42], and another study among U.S. adults found that increasing serum selenium levels were associated with decreased mortality up to 130 ng/ml and raised the concern that higher serum selenium levels beyond that might be associated with increased mortality [43]. Along with the previous studies, our study suggests that selenium supplementation may not be beneficial, especially for people already with a high selenium status.

Four other prospective studies have investigated dietary intake of other antioxidants (vitamin C, vitamin E, β-carotene, lycopene) in relation to pancreatic cancer, and all of them observed null or weak findings [20–22, 35]. Our study also observed null findings for these antioxidants, with one exception: we observed a decreased risk with the highest intake of β-carotene. The discrepancy with previous studies could be due to different populations or our finding could be due to chance.

This study has several strengths. The VITAL cohort is a prospective study designed specifically to investigate supplement use with cancer risk. Supplement users were targeted at recruitment to increase power as the recruitment letter described the study as one on supplement use and cancer risk, but the study was not restricted to supplement users. Information on supplementation was collected for the 10 years prior to base-line, providing

long-term intake. We collected extensive information on cancer risk factors, and we were able to carefully control for the potential confounding effects.

This study also has several limitations. Although our detailed supplement assessment yielded very good validity and reliability results [27], recall error from the self-reported food frequency questionnaire and supplement use was inevitable. Moreover, dietary selenium in food varies depending on where the food is grown (e.g. the selenium level in soil varies from 0.10 ppm to 1.31 ppm among counties in Washington [44]) and this information was not included in the determination of the selenium content of foods, so these non-differential measurement errors could have led to some attenuation of the results. Another limitation is that we examined a relatively large number of dietary exposures in this work, increasing the probability of a spurious result. Lastly, although we adjusted for education level and race in our final model, there may still be residual confounding from social-economic status. However, we do not think this a big concern because the current literature reveals only a weak or null association of social-economic status and pancreatic cancer risk [45–48]. In our analysis, further adjustment for household income did not change the conclusions.

In summary, our study did not observed an association between the use of antioxidant supplements and pancreatic cancer incidence. Our data suggest that dietary selenium is associated with reduced risk of pancreatic cancer, but the findings need replication in other populations.

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Table 1

Selected demographic characteristics, VITAL cohort, 2000–2008

	Mean	Std
Age (years)	61.99	7.45
BMI (kg/m^2)	27.41	5.17
Physical activity (MET, hr/wk)	10.88	13.89
Alcohol (g/d)	8.17	15.45
Total energy intake (kcal/day)	1855.12	773.95
	Frequency *	**%**
Sex		
Female	40225	51.94
Male	37221	48.06
Race		
White	72220	93.25
Others	5226	6.75
Education		
≤High school graduate	15377	20.2
Some college	29161	38.31
College or advanced degree	31587	41.49
Smoking status		
No	36459	47.46
Long-term quitters (>10 years)	28148	36.64
Current and short-term quitters (<=10 years)	12216	15.9
Family history of pancreatic cancer		
Yes	2834	3.71
No	73640	96.29
History of pancreatitis		
Yes	650	0.84
No	76777	99.16
History of Diabetes		
Yes	5411	6.99
No	72034	93.01

Abbreviations: BMI (body mass index), MET (Metabolic equivalent for all activities).

* Totals were not all equal to 77446 due to missing values.

Table 2

Association between average daily intake of dietary antioxidant and incident pancreatic cancer, VITAL cohort from 2000–2008

Antioxidant	Intake level	No. of subjects	No. of cases	Crude HR	P-trend	Adjusted HR*	P-trend
β-Carotene (mcg)	14.26– 2564.48	23440	66	1.00		1.00	
	2564.66– 4753.24	23441	54	0.81(0.57– 1.17)		0.81(0.56– 1.18)	
	4753.66– 59237.96	23441	42	**0.63(0.43– 0.93)**	0.13	**0.65(0.42– 0.99)**	0.29
Lutein+Zeaxanthin (mcg)	13.48– 1717.84	23440	62	1.00		1.00	
	1717.84– 3125.33	23441	56	0.90(0.63– 1.29)		0.92(0.63– 1.35)	
	3125.43– 100884.19	23441	44	0.71(0.48– 1.04)	0.54	0.74(0.48– 1.14)	0.84
Lycopene (mcg)	0– 3768.61	23440	67	1.00		1.00	
	3768.66– 7222.54	23441	47	0.70(0.48– 1.02)		0.79(0.54– 1.17)	
	7222.74– 218764.82	23441	48	0.72(0.50– 1.04)	0.07	0.82(0.53– 1.26)	0.25
Vitamin C (mg)	0.57– 76.64	23440	62	1.00		1.00	
	76.64– 135.01	23441	51	0.82(0.56– 1.18)		0.87(0.59– 1.28)	
	135.01– 1854.97	23441	49	0.79(0.54– 1.15)	0.17	0.89(0.58– 1.35)	0.51
Vitamin E (IU)	0.97– 9.24	23440	69	1.00		1.00	
	9.24– 14.93	23441	44	**0.64(0.44– 0.93)**		0.65(0.42– 1.01)	
	14.93– 303.22	23441	49	0.72(0.50– 1.03)	0.05	0.67(0.40– 1.12)	0.13
Selenium (mcg)	6.38– 85.49	23440	69	1.00		1.00	
	85.49– 127.50	23441	46	**0.67(0.46– 0.97)**		**0.58(0.35– 0.94)**	
	127.50– 641.60	23441	47	**0.68(0.47– 0.99)**	**0.04**	**0.44(0.23– 0.85)**	**0.01**
Zinc (mg)	1.45– 8.76	23440	61	1.00		1.00	
	8.76– 13.14	23441	48	0.79(0.54– 1.15)		0.90(0.56– 1.45)	
	13.14– 67.94	23441	53	0.87(0.60– 1.26)	0.57	0.94(0.52– 1.71)	0.98

*Models were adjusted for age, gender, ethnicity, education, body mass index, physical activity, cigarette smoking status, total alcohol consumption, family history of pancreatic cancer, history of diabetes and total energy intake.

Table 3

Association between 10-year mean daily antioxidant supplement use and incident pancreatic cancer, VITAL cohort from 2000–2008

Antioxidant	Intake level	No. of subjects	No. of cases	Crude HR	P-trend	Adjusted HR*	P-trend
Vitamin C (mg)	Non-user	20651	53	1.00		1.00	
	2.57– 148.57	28080	67	0.93(0.65– 1.34)		0.93(0.65– 1.34)	
	149.00– 1750.00	28083	59	0.82(0.56– 1.18)	0.53	0.82(0.56– 1.19)	0.44
Vitamin E (mg)	Non-user	20194	53	1.00		1.00	
	1.29– 100.86	28329	67	0.90(0.63– 1.29)		0.92(0.64– 1.32)	
	101.00– 1000.00	28328	64	0.86(0.60– 1.24)	0.80	0.80(0.55– 1.17)	0.37
Multi-Vitamin (pills)	Non-user	26732	70	1.00		1.00	
	0.04– 0.70	23934	54	0.86(0.60– 1.23)		0.95(0.66– 1.36)	
	0.79– 1.00	26770	60	0.86(0.61– 1.21)	0.34	0.81(0.57– 1.15)	0.14

*Models were adjusted for age, gender, ethnicity, education, body mass index, physical activity, cigarette smoking status, total alcohol consumption, family history of pancreatic cancer and history of diabetes.

Table 4

Association between total antioxidant intake (diet+10-year supplement use) and incident pancreatic cancer, VITAL cohort from 2000–2008

Antioxidant	Intake level	No. of subjects	No. of cases	Crude HR	P-trend	Adjusted HR*	P-trend
β-Carotene (mcg)	37.05– 4451.73	23172	60	1.00		1.00	
	4451.99– 8513.77	23173	53	0.88(0.61– 1.27)		0.86(0.59– 1.26)	
	8513.82– 109006.02	23172	42	0.70(0.47– 1.04)	**0.02**	0.69(0.46– 1.04)	**0.03**
Vitamin C (mg)	0.57– 137.20	23261	61	1.00		1.00	
	137.20– 347.25	23262	47	0.77(0.53– 1.12)		0.81(0.55– 1.20)	
	347.29– 2629.64	23262	49	0.80(0.55– 1.16)	0.44	0.82(0.56– 1.21)	0.46
Vitamin E (mg)	0.85– 18.35	23281	55	1.00		1.00	
	18.35– 70.45	23281	56	1.01(0.70– 1.47)		1.01(0.69– 1.47)	
	70.46– 524.95	23281	51	0.93(0.63– 1.36)	0.74	0.84(0.57– 1.24)	0.34
Selenium (mcg)	9.81– 98.76	23314	66	1.00		1.00	
	98.76– 145.65	23314	40	**0.61(0.41– 0.90)**		**0.59(0.37– 0.93)**	
	145.66– 646.60	23314	52	0.79(0.55– 1.14)	0.09	0.69(0.39– 1.20)	0.06
Zinc (mg)	1.73– 13.75	23273	55	1.00		1.00	
	13.75– 23.10	23273	56	1.02(0.71– 1.48)		1.04(0.71– 1.53)	
	23.10– 158.28	23273	46	0.84(0.57– 1.24)	0.31	0.81(0.53– 1.24)	0.24

*Models were adjusted for age, gender, ethnicity, education, body mass index, physical activity, cigarette smoking status, total alcohol consumption, family history of pancreatic cancer, history of diabetes and total energy intake.